Claim 51. (New) The DNA construct of claim 47, wherein the human DNA sequence comprises a coding sequence comprising a start codon having a 5'end and the first non-human sequence is joined adjacent to the 5' end of the start codon of the human DNA coding sequence.

Claim 52. (New) The DNA construct of claim 51, wherein the human DNA coding sequence comprises a stop codon having a 3' end and the first non-human sequence is joined adjacent to the 3' end of the stop codon of the human DNA coding sequence.

REMARKS

Claims 2, 15, 20, 26, and 42-43 have been canceled without prejudice or disclaimer. Claims 1, 8, 11, 14, 16, 18, 22-25, 32, 35, 39-41, and 44-46 have been amended. New claims 47-52 have been added. Subsequent to the entry of the present amendment, claims 1, 3-14, 16-19, 21-25, 27-41, and 44-52 are pending and at issue. These amendments and additions add no new matter as the claim language is fully supported by the specification and original claims.

I. Amendment to the Specification and Claims

Claims 1 and 14 have been amended to clarify that the DNA sequence is mouse rather than murine. Claim 46 has been amended to clarify that the embryogenic stem cell is from a mouse. Support for the amendments can be found throughout the specification and claims as filed, particularly at Figures 1-10; pgs. 8-9, **[0037]**; pg. 11, **[0048]**; pgs. 17-18, **[0081]-[0082]**; pg. 19, **[0088]** to pg. 22, **[0095]**; pg. 22, **[0099]-[0100]**; pg. 23, **[0102]**, **[0104]**; pg. 24, **[0105]**; pg 24, **[0107]-[0108]**; pg. 25, **[0110]**; and pg. 29, **[0124]**.

Claims 1, 8, 11, 18, 25, 45 have also been amended to clarify requisite steps and events in the methods claimed. Support for the amendments can be found throughout the specification and claims as filed, particularly at Figures 1-10 and the Examples describing the methods and constructs of the invention.

Claims 8, 11, 16, 22, 23, 24, 32, 35, 39-41, 44 have also been amended to correct antecedent basis errors, typographical errors, and for clarity. As such, these amendments add no new matter.

New claims 47-51 have been added. Claim 47 is identical to claim 18 except that it incorporates the limitations of claim 20 (now cancelled). Claims 48-51 depend from claim 47 and incorporate the limitations of claim 19, and 21-24. Accordingly, no new matter has been added by way of these additions and no new search is required.

II. Objections to the Claims

Claims 8, 26 and 41 have been objected to because of alleged informalities. According to the Examiner, "'oncogene gene'; 'suppressor gene gene'; and 'P450 gene gene' should be --oncogene--; -suppressor gene--; and --P450 gene-." Office Action at p. 3.

Claims 8, 26 and 41 have been amended to delete the second recitation of "gene."

Accordingly, withdrawal of the objection to claims 8, 26 and 41 is respectfully requested.

III. Information Disclosure Statement

The Office Action states, "[t]he information disclosure statement filed 5/10/04 failed to fully comply with 37 CFR 1.98(a)(2) because a copy of WO 01/11951 referred to therein had not been provided." According to the Examiner, Applicants arguments regarding the cumulative nature of the reference in question "are not germane to whether the IDS complied with 37 CFR 1.98(a)(2)."

Applicants respectfully disagree. In regard to preceding sections of the same regulation, 37 CFR §1.98(c) states:

> When the disclosures of two or more patents or publications listed in an information disclosure statement are substantively cumulative, a copy of one of the patents or publications as specified in paragraph (a) of this section may be submitted without copies of the other patents or publications, provided that it is stated that these other patents or publications are cumulative.

Applicants submit that the two patents at issue, WO 01/11951 and EP 1 206 906 Al, are substantively cumulative, and therefore, under 37 CFR §1.98(c) copies of both need not be submitted.

Applicants provided a copy of EP 1 206 906 Al (which the Examiner considered on October 27, 2005), in lieu of PCT publication WO 01/11951. The PCT publication had been listed in the International Search Report for related Application PCT/US03/28485, but was published in the Japanese foreign language, as evidenced by the front page, which was submitted with the IDS. Submission of substantially identical EP 1 206 906 Al obviated the need for

submitting an English language translation while fulfilling the duty to disclose art made known to the Applicant by the ISR..

Applicants acknowledge that the exact word "cumulative" as recited in 37 CFR §1.98(c), was not stated in the IDS. However, the IDS stated that WO 01/11951 was "also published as EP 1 206 906 Al." *See* Form PTO 1449 submitted on May 6, 2004, at pg. 1, line AB. Applicants submit that this statement carries the same meaning to the skilled artisan as the phrase "the two patents are cumulative." Therefore, Applicants submit that the provision of a copy EP 1 206 906 Al. as an English language equivalent complied with the duty to disclose WO 01/11951 according to the requirements of 37 CFR §1.98 and accordingly request acknowledgement to this effect.

However, if the Examiner insists that an IDS that contains the words "cumulative" must be filed, Applicants further submit that the May 6, 2004 IDS represents a *bona fide* attempt to comply with the requirements and request additional time under 37 CFR §1.97(f) to enable full compliance.

IV. Rejections under 35 U.S.C. §112, First Paragraph (Written Description

Claims 1, 3-14, 16, 17, 41, 43, and 44 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement in regard to the term "murine". Office Action at p. 3. According to the Examiner, "the term 'murine' is not

used at all in the original specification, and the term 'murine' does not mean 'mouse,' as implied by Applicant." *Id.*

Applicants submit that the rejection is moot in view of the amendment of independent claim 1 (from which claims 3-14, 16, 17, 41, 43, and 44 depend) to recite "mouse" instead of "murine." The recitation of "murine" in claim 14 has also been amended to "mouse."

Accordingly, withdrawal of rejection of claims 1, 3-14, 16, 17, 41, 43, and 44 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claim 45 has been rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Office Action at 4. According to the Examiner, the specification "describes only making non-human ES cells and transgenic animals, and fails to mention generic humanized non-human animal cells per se or methods of making them." *Id.*

Applicants respectfully traverse.

Applicants submit that the written description requirement does not demand *in haec verba* or *ipsis verbis* description. *See* MPEP 2163.I.A.l; *see also Fujikawa v. Wattanasin*, 93 F.3d 1559, (Fed. Cir. 1996); *All Dental Products, LLC v. Advantage Dental Products, Inc.*, 309 F.3d 774 (Fed Cir. 2002) ("In order to comply with the written description requirement, the specification 'need not describe the claimed subject matter in exactly the same terms as used in

the claims; it must simply indicate to persons skilled in the art that as of the filing date the applicant had invented what is now claimed."). Indeed, the written description requirement can be met by any of "express, implicit, or inherent disclosure." *Id.*

Applicants submit that the concept of "cell" is inherently described by the term "embryogenic stem cell." The skilled artisan would understand that the methods for making a humanized embryogenic stem cell are inherently methods for making a humanized cell, regardless of the type of cell that is humanized. Moreover, although the Examiner suggests that generation of a humanized animal other than a mouse was not possible at the time of invention, the Examiner has not demonstrated a similar void in the knowledge of the art regarding transfected non-human animal cells. At the time of invention, the art of introducing DNA constructs into an essentially limitless variety of human, non-human, animal and non-animal cells was very advanced. Thus, Applicants submit that the skilled artisan would appreciate that the inventors were in possession of the invention of generating a humanized cell by producing the recombined vector of claim 45.

Furthermore, it is well established in patent law that it is improper to limit an invention to a specific or preferred embodiment. The Federal Circuit has opined repeatedly on this issue. For example, in their recent opinon in *Phillips v. AWH Corp.*, 75 USPQ2d 1321, (Fed Cir. 2005), the court stated: "although the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments. *See, e.g., Nazomi Communications, Inc. v. ARM Holdings, PLC*, 403 F.3d 1364, 1369 [74 USPQ2d

1458] (Fed. Cir. 2005) (claims may embrace "different subject matter than is illustrated in the specific embodiments in the specification"); *Liebel-Flarsheim*, 358 F.3d at 906-08; Teleflex, 299 F.3d at 1327; *SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1121 [227 USPQ 577] (Fed. Cir. 1985). In particular, we have expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment. *Gemstar-TV Guide*, 383 F.3d at 1366. That is not just because section 112 of the Patent Act requires that the claims themselves set forth the limits of the patent grant, but also because persons of ordinary skill in the art rarely would confine their definitions of terms to the exact representations depicted in the embodiments." Similarly, Applicants submit that the skilled artisan would not limit the applicability of the methods of the invention for generating a humanized cell of claim 45 to only methods for humanizing mouse cells.

Finally, additional support for claim 45 can be found in the text of the specification. For example at page 6, **[0019]** stating: "The invention also provides a DNA construct for performing homologous recombination within a cell." Notably, this statement does not limit the cell to an embryogenic cell. Furthermore, the same paragraph describes using ES cells as only "one embodiment." At page 6, **[0020]** the specification states "the invention provides a method for generating a DNA construct for performing homologous recombination within a cell" Differentiating that statement, the same paragraph states that the "DNA construct that is produced can then be introduced into a non-human ***embryogenic stem*** cell." Applicants submit

that the recitation of "cell" in paragraph **[0020]** clearly contemplates that the methods could be used to generate a broader group of humanized cells than simply ES cells.

Applicants submit that although one embodiment of the invention relates to humanized embryonic stem cells, the specification more than adequately describes humanizing cells other than embryonic stem cells to the skilled artisan as required under 35 U.S.C. §112, first paragraph.

Accordingly, withdrawal of rejection of claim 45 under 35 U.S.C. §112, first paragraph, is respectfully requested.

V. Rejections under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 1, 3-14, 16, 17, 25, 27-41 and 43-46 stand rejected under 35 U.S.C. §112, first paragraph as allegedly being non-enabled for embodiments other than those enumerated by the Examiner. Office Action at 4. Specifically, the Examiner asserts that the only enabled embodiments are those "wherein the non-human animal is a mouse, the non-human animal DNA of the first construct is a mouse genomic DNA comprising mouse DNA, which is orthologous to the human DNA sequence of the second and third constructs, that is immediately flanked by first and second mouse genomic sequences that are essentially identical to the flanking first and second mouse genomic DNA sequences, respectively, that flank the human DNA sequence in the second construct, the embryogenic stem (ES) cell is a mouse ES cell, the non-human blastocyst is a

mouse blastocyst, and the pseudopregnant non-human animal is a pseudopregnant mouse." *Id.* at 4-5.

Applicants submit that the rejection as applied to claims 1, 3-14, 16, 17, 41, and 43-44 is moot in view of the amendment to claims 1, 14 and 46, specifying "mouse" DNA sequences and embryonic stem cells.

With respect to claims 25, 27-40 and 45, Applicants respectfully traverse.

The crux of the Examiner's argument appears to be that the "at the time of filing, the state of the art held that targeted gene disruption could only be carried out in mouse." As described above in section **IV**, it appears that the Examiner again is attempting to limit the invention to a single disclosed embodiment, without consideration of the knowledge of the skilled artisan in applying the teaching of the invention. Specifically, the Examiner appears to argue that the only application disclosed, contemplated or available in the art for the methods of the invention of generating humanized cells is in generating complete, humanized animals.

Applicants submit that both the use and desirability of gene targeting in somatic cells, including non-human and non-mouse cells, was well known in the art at the time of the present invention. For example, humanization of antibody genes was well-known in the art in 2002, and at least some interest in humanizing antibody genes, including those hybridoma cells (somatic cells) by homologous recombination existed. *See, e.g.*, Carter *et al., Proc. Natl. Acad. Sci. USA* 89:4285-89, 1992, attached hereto as Exhibit A; Baker, *et al., Proc. Natl. Acad. Sci. USA* 88:6432-36, 1988, attached hereto as Exhibit B). Furthermore, it was known in the art that

homologous recombination occurs in various types of somatic cells, such as RAT-2tk$^-$ cells and LMtk$^-$ (*see e.g.*, Folger et al., *Mol Cell. Biol.* 2:1372-87, 1982; attached hereto as Exhibit C), and that replacement of non-human genes with humanized versions was of interest for elucidating the functional differences between proteins (*see e.g.,* Smith and Kalogerakis, *Nucl. Acids Res.* 19:7161-70, 1991; attached hereto as Exhibit D) and for production of human proteins for therapeutic purposes. *See e.g.,* De Strooper *et al., EMBO J.* 14:4932-4938, 1995, attached hereto as Exhibit E.

The Examiner acknowledges that at least one embodiment of the methods of the invention is expressly enabled by the specification. (*i.e.,* use of homologous recombination vectors for gene targeting in mice). Applicants submit that additional applications, for example gene targeting in somatic cells, would be well within knowledge of skill in the art and could be accomplished using exactly the same procedures and teachings of specification for gene targeting in mouse ES cells.

In addition, the Examiner notes the alleged "undue breadth of the identity of the murine or non-human animal DNA sequences and the human DNA sequences...would be overcome by limiting (in claims 1, 25, and 45) the non-human DNA in the first construct and first and second non-human animal DNA of the second and third construct to all be DNA from the same non-human animal, and the cell to be from that same non-human animal." Office Action at p. 10. The Examiner further suggest that "limiting the murine/non-human DNA sequence of the first construct to comprise" certain sequence components in a required order. *Id.*

Applicants submit that the amendments to the claims embody the Examiner's suggestions, although the language may vary slightly from that suggested.

Accordingly, reconsideration and withdrawal of the rejection of claims 1, 3-14, 16, 17, 25, 27-41 and 43-46 under 35 U.S.C. §112, first paragraph, is respectfully requested.

VI. Rejections under 35 U.S.C. §112, Second Paragraph

Claims 11-14, 16-24, 35-38, 43 and 44 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Office Action at p. 10.

Claims 20 and 43 have been cancelled. Claims 11, 16, 18, 22, 23, 24, 35 and 44. have been amended to address antecedent basis issues and for clarity, as suggested by the Examiner. Claims 12-14, 17, 19, 21 depend from the amended claims 11, 16, 18, 22, 23, 24, 35 and 44. Applicants submit that the amendments to the claims remediate the indefiniteness issues raised by the Examiner.

Accordingly, withdrawal of rejection of claims 11-14, 16-24, 35-38, 43 and 44 under 35 U.S.C. §112, second paragraph, is respectfully requested.

VII. Rejection under 35 U.S.C. §102

Claims 18, 21-24, 41 and 43 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Divoky *et al.* (*Proc. Natl. Acad. Sci. USA* 98:986-991, 2001). Office Action at 12.

Applicants submit that the rejection of claims 18, 21-24,41 and 43 is moot in view of the amendments to the claims.

Base claim 18 has been amended to incorporate the limitations of non-rejected claim 20, now cancelled, while new claim 47 is identical to claim 18, except that it incorporates the limitations of non-rejected claim 19 . Applicants note that the Examiner did not find claims 19 and 20 anticipated by Divoky *et al.* and therefore incorporating the limitations of these claims into independent claim 18 overcomes the rejection. Claims 21-24 depend from amended claim 18, while new claims as well as new claims 49-52 depend from new claim 47, incorporating the limitations of claim 21-24, respectively.

Regarding claims 41, Applicants submit that EPO is characterized as a hormone and the EPO receptor is accordingly a hormone receptor. *See* Winkelman et al.Blood 76:24-30, at pg. 24,1990; attached hereto as Exhibit F. Claim 41 has been amend to delete the hormone receptor gene from the list of human DNA sequences. Thus, the mouse of Divoky *et al.* is not encompassed by claim 41 as amended.

Regarding claim 43, the Examiner states "[t]o the extent that EPO is a drug used in humans and the EPO receptor is involved in metabolism of EPO, it meets the limitations of claim 43." Office Action

Applicants submit that EPO is not a drug, but is a biologic. This distinction is recognized, for example, by the FDA, which has different divisions assigned to the regulation and approval of drugs and biologics. When construed in light of the specification, Applicants submit that the term drug has a meaning consistent with that distinction. The Examiner's definition is contrived. The EPO receptor of Divoky *et al.* is involved in erythropoiesis – not drug metabolism. Furthermore, claim 41 as amended, from which claim 43 depends, is not anticipated by Divoky *et al.*. Taken together, Applicants submit that claim 43 as amended, is not anticipated by Divoky *et al.*.

Accordingly, withdrawal of rejection of claims 18, 21-24, 41 and 43 under 35 U.S.C. §102(b) is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if it is believed that prosecution can be assisted thereby.

A check in the amount of $60.00 is enclosed as payment for the one-month Extension of Time fee. No other fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

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